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ORIGINAL RESEARCH

STRUCTURAL

Heterotopic Crosscaval Transcatheter Tricuspid Valve Replacement for Patients With Tricuspid Regurgitation

The Trillium Device

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ABSTRACT

BACKGROUND Transcatheter tricuspid interventions are an emerging therapy for patients with severe tricuspid regurgitation (TR), but a significant proportion of patients with TR are unsuitable for orthotopic tricuspid valve (TV) approaches.

OBJECTIVES The aim of this study was to investigate the performance of a dedicated heterotopic valve replacement system in patients with severe or greater TR.

METHODS This single-arm, multicenter study assessed the technical performance, efficacy, and safety of heterotopic cross-caval transcatheter TV replacement using the Trillium device at 30 days. Patients with severe or greater TR ineligible for surgical or other interventional orthotopic TV treatment were included.

RESULTS Between 2021 and 2023, 20 patients (median age 81 years, 40% women) were included. Device implantation was successful in all cases, and no intraprocedural deaths or conversions to surgery occurred. Postprocedurally, central venous pressure was reduced (median −3 mm Hg; Q1-Q3: −5 to −1 mm Hg; $P = 0.003$), and TR severity as assessed at the level of the Trillium device was reduced in all cases ($P < 0.001$). Within the 30-day follow-up period, 1 patient died, 2 patients experienced heart failure hospitalization, 2 required hemodialysis, and 2 experienced major bleeding. There was an improvement in NYHA functional class ($P = 0.005$) and a trend toward a reduction in edema severity score (median −0.5; Q1-Q3: −1 to −0; $P = 0.052$).

CONCLUSIONS The Trillium device is a safe and effective device for the treatment of patients with severe or greater TR ineligible for other therapeutic options. The device leads to a hemodynamic and symptomatic improvement of the burden of TR, whether this translates into favorable outcomes is to be proven in randomized trials.

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ABBREVIATIONS AND ACRONYMS

CVP = central venous pressure

KCCQ = Kansas City Cardiomyopathy Questionnaire

RA = right atrial/atrium

RV = right ventricle/ventricular

TEER = tricuspid valve edge-to-edge therapy

TR = tricuspid regurgitation

TTVI = tricuspid valve intervention

TV = tricuspid valve

Tricuspid regurgitation (TR) is associated with significant morbidity and mortality but foremost a potpourri of severe symptoms that range from conventional heart failure symptoms such as dyspnea and limited functional capacity to malnutrition, abdominal bloating, and ascites associated with systemic effects of TR.[1-3] In light of the high symptomatic burden of patients with severe TR, it becomes evident that treatment of TR is crucial to alleviate continuous impairment in quality of life.[2]

Orthotopic approaches such as repair using tricuspid valve (TV) edge-to-edge therapy or transcatheter TV replacement technologies have been introduced and safety validated in clinical trials.[4] Although TV edge-to-edge repair (TEER) represents the most widely used therapeutic approach for transcatheter TV intervention (TTVI), this approach is limited to patients with suitable anatomy and foremost graspable gap sizes, which even with improvements in techniques and device technology represent major limitations especially in patients with advanced disease stages.[5,6] With respect to orthotopic TV replacement, recent real-world data suggested that almost 75% of patients referred were not suitable for this treatment approach.[7] Heterotopic approaches have been proposed as an alternative therapeutic option, as those devices are mostly independent of anatomical considerations of the right ventricle (RV) and tricuspid annulus and while they "sacrifice" the right atrium (RA) and tolerate high-grade regurgitant volume from the RV to the RA, they possibly abolish systemic effects of severe TR. Initial approaches with nondedicated devices have shown conflicting results, leading to the development of dedicated devices for heterotopic TTVI.

Here we present the initial results for the Trillium device (Innoventric), a dedicated heterotopic TTVI, and report on the safety, technical performance, and efficacy of the device at 30 days.

METHODS

TRIAL DESIGN AND INCLUSION AND EXCLUSION CRITERIA. This was a prospective, single-arm, multicenter first-in-human study to evaluate the safety and performance of the Trillium stent graft system. Twenty patients at 9 investigational sites were enrolled. All patients were assessed at baseline, during the procedure, at discharge, and after 1 month following the index procedure (Supplemental Figure 1).

The study was intended for adult patients with severe, symptomatic, primary, or functional TR who were deemed to be appropriate candidates for transcatheter placement of a cross-caval stent graft.

The full inclusion and exclusion criteria are shown in Supplemental Table 1. The Trillium first-in-human study was approved by local ethics committees and the respective health authorities of the participating countries. All subjects provided written informed consent. The study is registered at ClinicalTrials.gov (NCT04289870).

THE TRILLIUM DEVICE. Trillium is a cross-caval covered stent graft with a valved wall that spans the RA with one end fixed in the superior vena cava and the other end fixed in the inferior vena cava (**Figure 1**). Details on the device and implantation procedure are provided in the Supplemental Appendix (Video 1).

ENDPOINTS. The primary endpoint with regard to safety was the rate of device- or procedure-related major adverse events (including mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications, conduction disturbances and arrhythmias, and other valve-related complications), as well as freedom from unplanned surgery or reintervention because of life-threatening device or procedure failure. Technical performance was defined as successful access, delivery, and retrieval of the Trillium delivery system. As an efficacy endpoint, TR grade as measured on the device valves (echocardiography), by hepatic vein systolic backflow

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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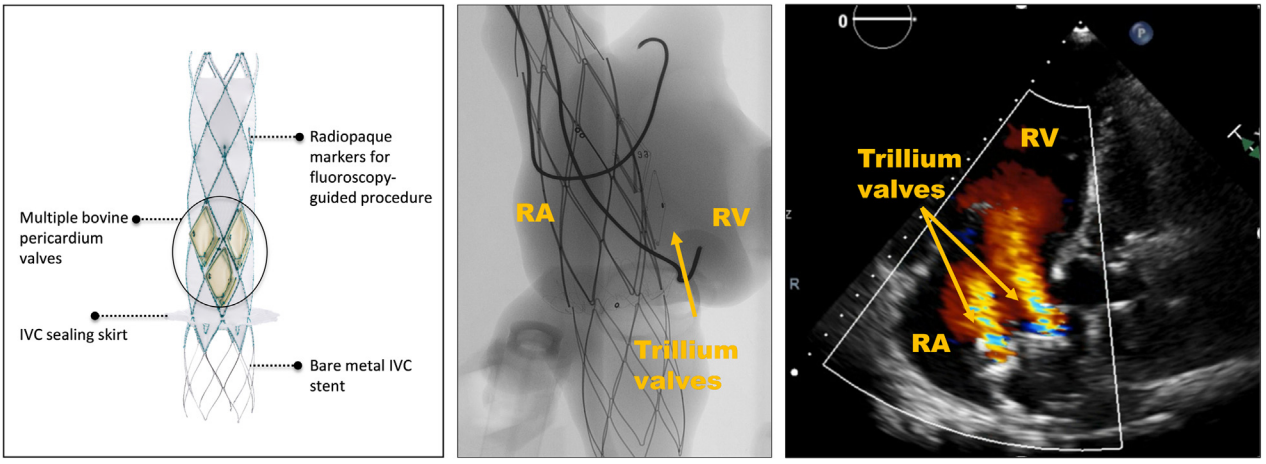
FIGURE 1 **The Trillium Device**



Key features of the trillium valve (left), example placement of the Trillium valve in a model illustrating fluoroscopic features (middle), and function of the Trillium valve during diastole showing inward flow from the prosthesis to the right atrium (RA) and right ventricle (RV) through the Trillium valves. IVC = inferior vena cava.

(echocardiography), or by reduction in central venous pressure (CVP) (invasive hemodynamic measurement) at the end of the procedure was analyzed. Furthermore, quality of life was assessed in an exploratory fashion by using the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ). All clinical events were defined according to Valve Academic Research Consortium-2 criteria.[8] Postimplantation syndrome was defined as elevated leukocyte and C-reactive protein levels without clinical evidence of bacterial or viral infection.

STATISTICAL ANALYSIS. Continuous data are expressed as median (Q1-Q3). In case of missing data, we provide the number of events or the corresponding mean or median and the number of available variables. Continuous variables were compared using the Wilcoxon signed rank test when paired or the Mann-Whitney *U* test when unpaired.

A 2-sided significance level of $\alpha = 0.05$ was defined as appropriate to indicate statistical significance. Statistical analyses were performed using SPSS version 25.0 (IBM).

RESULTS

Overall, 20 patients from 9 centers were included in the present study (Supplemental Figure 2). All patients were not suitable for either TEER or orthotopic TTVI. Baseline characteristics are shown in **Table 1**. The patients had typical features of patients with TR undergoing percutaneous interventions, consisting of advanced age (median 81 years; Q1-Q3: 76-83 years), increased perioperative surgical risk (median TRI-SCORE 6 points; Q1-Q3: 5-7 points), high rate of atrial fibrillation (20 of 20 [100%]), elevated N-terminal pro-brain natriuretic peptide (median 2,347 pg/mL; Q1-Q3: 1,092-4,227 pg/mL), and impaired renal function (median estimated glomerular filtration rate 41 mL/min/1.73 m^2; Q1-Q3: 33-56 mL/min/1.73 m^2). Patients in the present study presented with severely advanced heart failure, with all patients being in NYHA functional class III or IV, a substantial rate of ascites (6 of 20 [30%]), high symptomatic burden (median KCCQ score 42 points; Q1-Q3: 28-58 points), a high rate of previous heart failure hospitalization (16 of 20 [80%] 1 year before study inclusion), and a median CVP v-wave of 28 mm Hg. The presence of complex anatomy is highlighted by previous failed interventional attempts in 30% (6 of 20), transvalvular leads in 40% (8 of 20), and a median coaptation gap of 11 mm and annular diameter of 53 mm.

PROCEDURAL RESULTS. Device implantation was successful in all cases. The access site for all procedures was the right femoral vein, with a median skin-to-skin time of 22 minutes (Q1-Q3: 17-35 minutes), a median device deployment time of 6 minutes (Q1-Q3: 4-8 minutes), and a median contrast volume of 78 mL (Q1-Q3: 56-98 mL). No conversion to open surgery was necessary. No intraprocedural deaths occurred.

Hemodynamically, there was a significant reduction in CVP, with a mean CVP of 19 mm Hg (Q1-Q3: 15-24 mm Hg) being reduced by −3 mm Hg

TABLE 1 Baseline Characteristics (N = 20)

Age, y	81 (76-83)
Female	8 (40)
BMI, kg/m^2	26 (23-29)
EuroSCORE II, %	5.1 (4.0-12.7)
TRI-SCORE, points	6 (5-7)
Symptoms	
NYHA functional class	
II	0
III	19 (95)
IV	1 (5)
6MWD, m	194 (154-287)
Edema severity score	2 (1, 3)
KCCQ score, points	42 (28-58)
Ascites	6 (30)
Chronic liver disease	9 (45)
Medical history	
Previous HF hospitalization with 1 y	16 (80)
Previous CABG	2 (10)
Previous cardiac surgery	6 (30)
Previous tricuspid valve intervention	6 (30)
Edge-to-edge repair	5 (25)
Annuloplasty	1 (5)
Lung disease	4 (20)
Atrial fibrillation	20 (100)
Transtricuspid lead	8 (40)
Loop diuretic furosemide dose, mg/day	60 (40-200)
Mineralocorticoid receptor antagonist	14 (70)
Laboratory measurements	
NT-proBNP, pg/mL	2,347 (1,092-4,227)
eGFR, mL/min/1.73 m^2	41 (33-56)

Values are median (Q1-Q3) or n (%).

6MWD = 6-minute walk distance; BMI = body mass index; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-brain natriuretic peptide.

(Q1-Q3: −5 to −1 mm Hg), and a median v-wave of 28 mm Hg (Q1-Q3: 22-37 mm Hg) being reduced by −9 mm Hg (Q1-Q3 −12 to −4 mm Hg), while expectedly, RA pressure increased. Acutely, there were no changes in pulmonary artery pressures or cardiac output (Central Illustration, Table 2). Postinterventional anticoagulation was managed with vitamin K antagonists in all patients. Additionally, 3 patients received concomitant platelet inhibition, with aspirin prescribed for 1 patient and clopidogrel for 2 patients.

ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline and follow-up echocardiographic parameters are displayed in Table 3 and Figure 2. Patients showed relevant TR at baseline, with most patients having torrential TR. Patients had severe RV dilatation but mainly preserved systolic RV function as assessed by tricuspid annular plane systolic excursion and RV fractional area change and patients presented with preserved left ventricular ejection fraction at baseline.

Postimplantation, there was 1 case of mild paravalvular inferior vena cava leak. No other cases of paravalvular reflux were observed. No cases of leaflet thrombosis were observed. TR as assessed on the Trillium level was reduced to mild in all patients at discharge as well as at last available follow-up, as displayed in the Central Illustration. Although effective regurgitant orifice area was not affected by device placement, there was a significant reduction in regurgitant volume and, interestingly, a reduction in TR severity. RV dimensions were not significantly affected acutely by the treatment. RV function as assessed by tricuspid annular plane systolic excursion and RV fractional area change did not deteriorate after treatment. Left ventricular function and dimension was not affected by TR treatment.

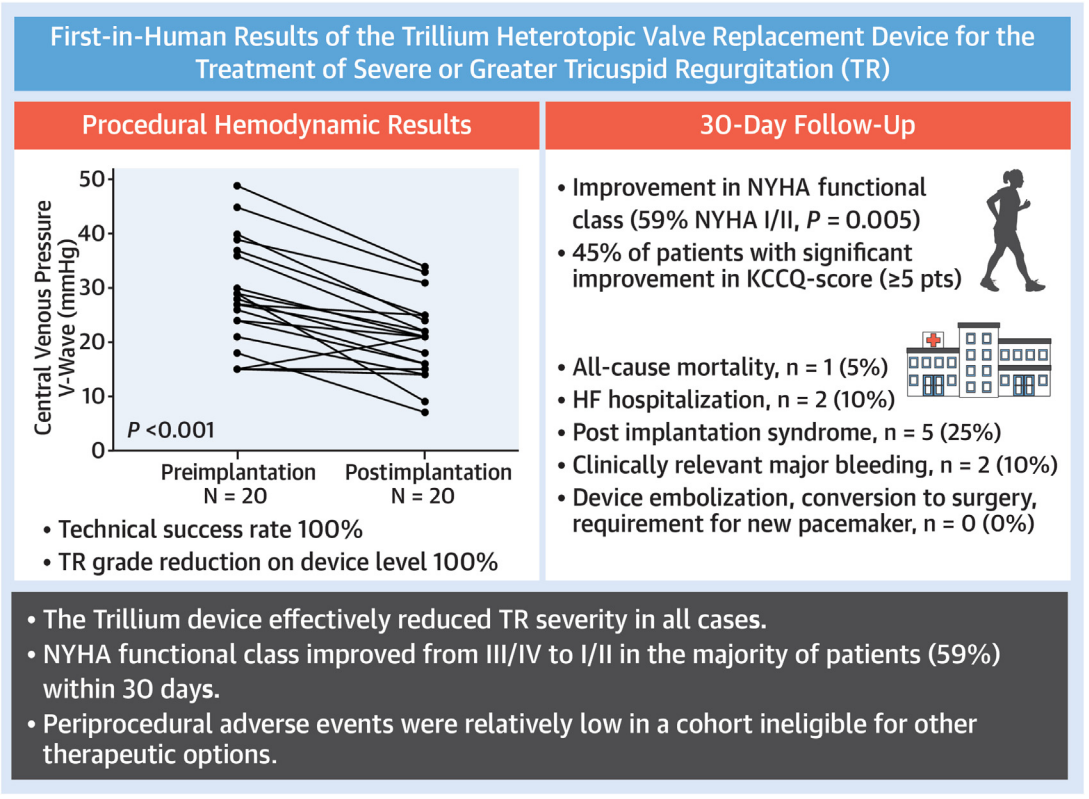
CLINICAL OUTCOMES. Clinical events within the follow-up of 30 days are shown in Table 4. Within this follow-up period, 1 patient died of progressive heart and multiorgan failure after refusing further therapy.

Two patients experienced heart failure hospitalization, 2 had renal failure requiring hemodialysis, and 2 experienced major gastrointestinal bleeding events requiring either intervention or blood transfusion. The most frequent adverse event was postimplantation syndrome manifested by elevated leukocyte and C-reactive protein levels for an average of 4 days, which occurred in 5 patients.

SYMPTOMATIC IMPLICATIONS. At 30-day follow-up, there was a significant improvement in NYHA functional class (Figure 3A) and a borderline significant reduction in the edema severity score (Figure 3B). There was a nonsignificant increase in 6-minute walk distance (Figure 3C), and there was a nonsignificant increase in KCCQ score (median improvement 7 points; Q1-Q3 −12 to 29 points) (Figure 3D). At 30 days, KCCQ score showed a clinically relevant improvement (change in KCCQ score ≥5 points) in 9 of 20 patients (45%).

LABORATORY CHANGES. Impaired renal function at baseline did not change in the time course of 30 days. There was a significant decrease in hemoglobin over the initial time course. Furthermore, there was a reduction in bilirubin as well as a borderline significant reduction in alanine transaminase, while aspartate transaminase and gamma-glutamyl transferase did not change significantly. Lactate dehydrogenase and N-terminal pro-brain natriuretic peptide increased significantly (Table 3).

CENTRAL ILLUSTRATION **Early Clinical Performance of the Trillium Heterotopic Valve Replacement System**



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The Trillium device led to a reduction in central venous pressure v-wave and showed good technical success and safety, while being associated with improvements in functional parameters of patient well-being. HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; TR = tricuspid regurgitation.

DISCUSSION

We report the results of the first 20 patients treated with the Trillium device, a dedicated heterotopic cross-caval transcatheter TV replacement device. The main findings of the study are as follows: 1) in this cohort of patients with advanced TR and heart failure deferred from other TR treatment options, the Trillium device showed a favorable safety profile, with a 30-day mortality rate of 5%; 2) heterotopic transcatheter TV replacement led to a hemodynamic relief of backward failure by reducing CVP; and 3) in short-term follow-up, there was a significant reduction in heart failure-related symptoms and a trend toward a reduction in heart failure signs as well as improvements in quality of life.

The present cohort, which represents the initial experience with the Trillium device, likely represents the most advanced disease stage group in the field of interventional TR treatment. Previous heart failure hospitalization rates were significantly higher compared with prospective trials in the field of TEER[9,10] and orthotopic TTVI.[11] Patients presented with severe symptomatic right heart failure, with one-third of patients already experiencing clinically evident ascites. From an anatomical point of view, there was a large number of patients with torrential TR, large RV dimensions, and tricuspid annular dimensions, with transtricuspid leads being present in 40% of patients and one-third of patients having experienced previous interventional TR repair approaches. In comparison with the TRILUMINATE trial, patients in the present study had higher CVP (12 mm Hg vs 19 mm Hg), higher effective regurgitant orifice area (0.7 cm^2 vs 1.1 cm^2), more previous heart failure hospitalizations (25% vs 80%), more impaired quality of life (KCCQ score 56 points vs 42 points), and higher rates of transtricuspid leads (16% vs 40%).[9]

TABLE 2 Changes in Hemodynamics

	Pre (n = 20)	Post (n = 20)	*P* Value
CVP mean, mm Hg	19 (15-24)	17 (13-20)	0.003
CVP v-wave, mm Hg	28 (22-37)	21 (15-25)	<0.001
RAP mean, mm Hg	16 (13-22)	20 (15-26)	0.087
RAP v-wave, mm Hg	27 (19-30)	34 (25-48)	0.001
RVEDP, mm Hg	9 (4-15)	10 (5-18)	0.83
RVESP, mm Hg	43 (32-48)	45 (36-49)	0.49
PAP systolic, mm Hg	42 (39-54)	47 (39-56)	0.41
PAP diastolic, mm Hg	21 (17-23)	19 (13-25)	0.93
PAP mean, mm Hg	29 (25-33)	28 (20-34)	0.85
PCWP, mm Hg	18 (14-20)	–	
Cardiac output, L/min	4.6 (3.5-6.5)	4.9 (3.6-6.8) (n = 16)	0.62

CVP = central venous pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; RVESP = right ventricular end-systolic pressure.

Despite all these factors, heterotopic cross-caval transcatheter TV replacement proved to be a safe and effective therapeutic option for these patients. Although in-hospital mortality was not as low as seen in randomized TEER trials such as TRILUMINATE (0%)[9] or TRI-Fr (0.6%),[10] the in-hospital mortality rate of 5% observed in the current population is well in line with real-world data for orthotopic valve replacement (5.0%[7]) as well as other dedicated trials for heterotopic valve devices such as the TricValve (5.7%[12]). This is especially interesting given the background of high symptomatic burden and disease severity in this subgroup of patients with TR, which was observed in the present cohort but has already been described for patients deferred from orthotopic valve replacement.[7] Last, the procedure proved its practicability with short procedural durations, no device migrations, the possibility to be performed without general anesthesia or intraprocedural

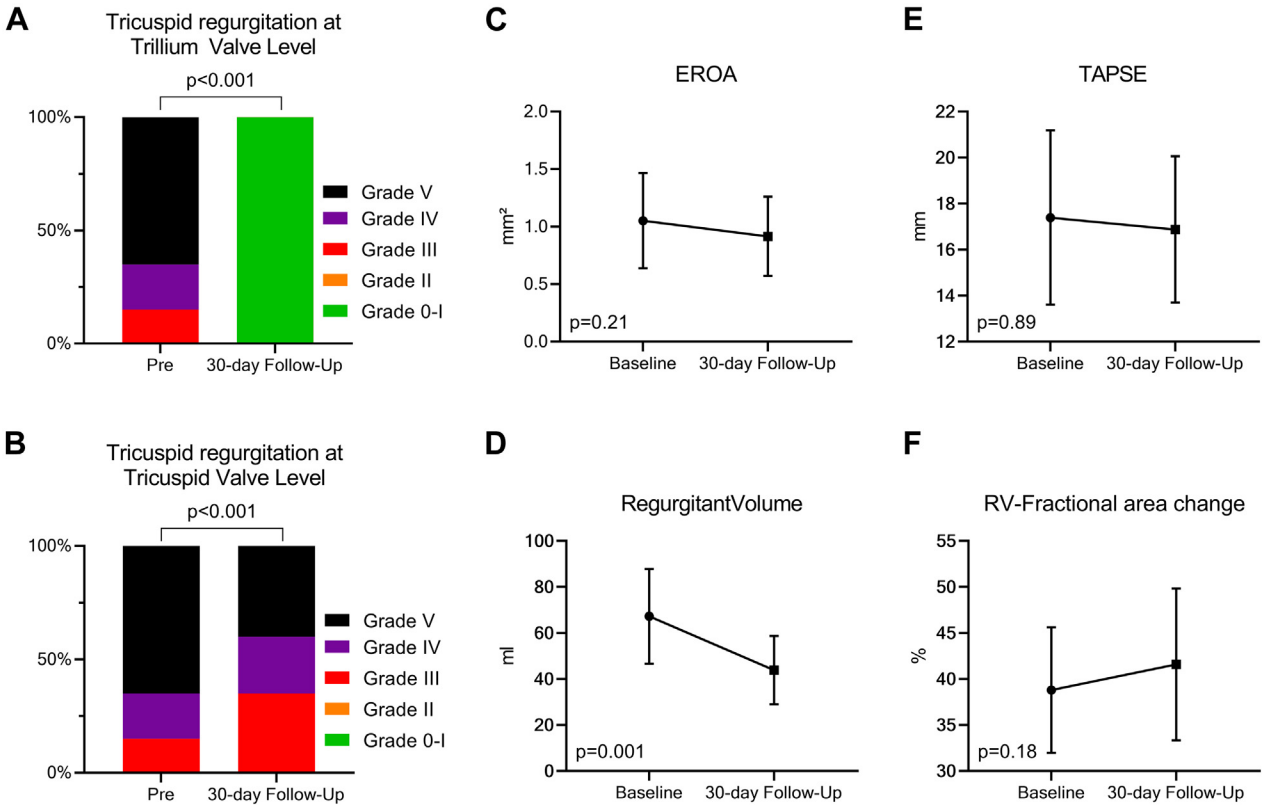
TABLE 3 Changes in Echocardiographic and Laboratory Values at 30 Days

	Pre (n = 20)	Δ Post	*P* Value
TR EROA, mm^2	1.1 (0.6-1.3)	−0.1 (−0.3 to 0.1) (n = 16)	0.21
TR regurgitant volume, mL	61 (51-83)	−22 (−35 to −7) (n = 16)	0.001
RV basal diameter, mm	59 (52-67)	0 (−8 to 6) (n = 17)	0.52
RV mid diameter, mm	46 (40-56)	−1 (−7 to 9) (n = 17)	0.85
RV longitudinal diameter, mm	78 (73-84)	−2 (−5 to 2) (n = 17)	0.30
RV end-diastolic area, mm^2	33 (29-48)	1 (−8 to 6) (n = 17)	0.85
RV end-systolic area, mm^2	20 (17-27)	−1 (−7 to 3) (n = 17)	0.47
LV end-diastolic diameter, mm	49 (42-52)	−2 (−4 to 4) (n = 17)	0.76
RA diameter, mm	69 (59-74)	4 (−6 to 11) (n = 17)	0.27
RA area, mm^2	48 (40-56)	0 (−6 to 7) (n = 17)	0.86
LVEF, %	63 (55-74)	1 (−9 to 6) (n = 17)	0.98
TAPSE, mm	17 (14-20)	0 (−3 to 2) (n = 17)	0.89
Cardiac output, L/min	3.7 (2.4-5.4)	0.3 (−0.8 to 1.2) (n = 17)	0.48
RVFAC, %	39 (33-44)	3 (−3 to 10) (n = 17)	0.18
Laboratory values			
Creatinine, mg/dl	1.4 (1.2-1.6)	0 (−0.3 to 0.3) (n = 18)	0.94
GFR, mL/min/1.73 m^2	41 (33-56)	1 (−3 to 13) (n = 17)	0.26
BUN, mg/dl	44 (24-81)	−2 (−21 to 12) (n = 14)	0.78
White blood cell count, $\times 10^3/\mu L$	6.1 (4.6-8.0)	0.3 (−0.8 to 1.1) (n = 17)	0.39
Red blood cell count, $\times 10^6/\mu L$	3.9 (3.4-4.5)	−0.4 (−0.7 to −0.1) (n = 18)	0.001
Hemoglobin, g/dL	11.5 (9.6-12.5)	−0.8 (−1.4 to −0.4) (n = 17)	0.029
Hematocrit, %	36 (30-38)	−3 (−5 to −1) (n = 17)	0.001
Bilirubin, mg/dl	0.7 (0.6-0.9) (n = 19)	−0.1 (−0.3 to 0) (n = 14)	0.021
ALT, U/l	20 (12-25)	−1.8 (−9.6 to 0.5) (n = 17)	0.088
AST, U/l	30 (21-39)	−0.6 (−6.5 to 4.8) (n = 16)	0.54
gGT, U/l	125 (54-214)	14 (−32 to 70) (n = 17)	0.27
LDH, U/l	256 (186-278) (n = 18)	50 (18-121) (n = 17)	0.004
NT-proBNP, pg/mL	2,347 (1,092-4,227)	550 (−140 to 2,511) (n = 17)	0.019

Values are median (Q1-Q3).

ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; EROA = effective regurgitant orifice area; GFR = glomerular filtration rate; gGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; RA = right atrial; RV = right ventricular; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

FIGURE 2 **Changes in Tricuspid Regurgitation Severity and Right Ventricular Function**



Changes in tricuspid regurgitation at the Trillium valve level (A) and the valve level (B), (C) effective regurgitant orifice area (EROA), (D) regurgitant volume, (E) tricuspid annular plane systolic excursion (TAPSE), and (F) right ventricular (RV) fractional area change. For (C) to (F), point estimates represent mean values and error bars indicate ±SD.

TABLE 4 **Clinical Events Within 30 Days (N = 20)**

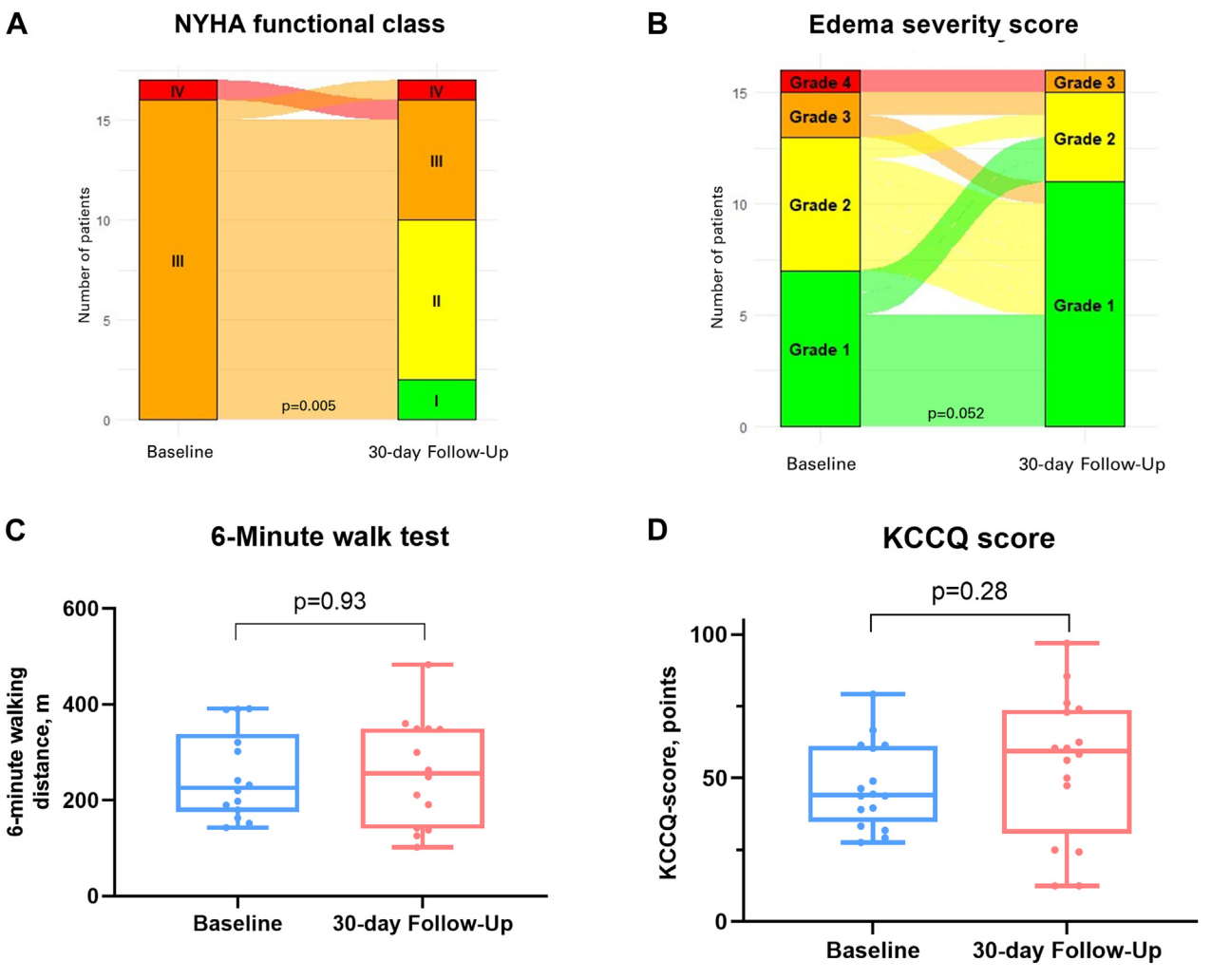
Death	1 (5)
Heart failure hospitalization	2 (10)
Myocardial infarction	0
Stroke	0
Conduction disturbances requiring pacemaker implantation	0
Postimplantation syndrome	5 (25)
Renal failure leading to dialysis	2 (10)
Clinically relevant major bleeding	2 (10)
Gastrointestinal bleeding	2 (10)
Technical success	20 (100)
Device embolization/migration	0 (0)
Paradevice leak	1 (5)
Conversion to surgery	0 (0)
Cardiac tamponade	0 (0)
Length of in-hospital stay, d	11 (7-14)

Values are n (%).

echocardiography, and a 100% technical success rate even in this early adaptive state. Furthermore, no stent fractures or device-related complications, such as thrombosis of the stent graft openings or valves, occurred. In patients with transtricuspid leads, no dislodgements or issues on pacemaker interrogation were reported. This study successfully shows that heterotopic valve replacement is not hindered by cardiac chamber dimensions or TR severity and has shown good performance in this patient population, which currently has limited therapeutic options but severe symptomatic burden.

The concept of heterotopic transcatheter TV replacement is still under debate. Backward failure is one of the most important and also detrimental sequelae of severe TR and affects both outcomes and symptoms.[13,14] More specifically, chronic venous congestion causes congestive nephropathy, hepatopathy, gastropathy, and intestinal edema with consequent malabsorption.[1,13] The significant reduction in

FIGURE 3 **Changes in Symptoms in Patients Being Treated With Heterotopic Valve Replacement With the Trillium Device**



Paired data showing changes in (A) NYHA functional class, (B) edema severity score, (C) 6-minute walk distance, and Kansas City Cardiomyopathy Questionnaire (KCCQ) score before and 30 days after transcatheter heterotopic valve replacement in patients with relevant tricuspid regurgitation.

CVP observed following Trillium implantation is crucial, as the concept of heterotopic valve replacement aims at reducing venous congestion, which is driven mainly by TR volume that leads to increased CVP. Allegedly, if CVP is not reduced, improvements in subsequently affected organs might not be expected. Alongside this, a reduction in bilirubin and alanine transaminase in the present cohort was observed. Although both TEER[15-17] and orthotopic valve replacement[4] reportedly lead to increases in effective RV stroke volume and output, whether this effect can be observed in heterotopic valve replacement remains to be seen in larger cohorts.[12] The main determinant of impaired cardiac output in patients with severe TR is considered to be the regurgitant volume, so reducing regurgitation should therefore enhance cardiac output. In a proportion of our patients, Trillium implantation led to a reduction of TR at the level of the TV. This might be explained by an increase in RA pressures, consequently reducing the pressure gradient between the RV and RA. Although heterotopic cross-caval transcatheter TV replacement aims at improving the detrimental effects of backward failure, there might be also beneficial effects on forward failure, which need to be assessed in the future. Furthermore, another study of heterotopic valve replacement demonstrated favorable RV reverse remodeling with reduction of RV end-diastolic volume, indicating restoration of preload reserve.[18]

It seems that aforementioned hemodynamic alterations might translate into symptomatic alleviation, as there was a significant reduction with regard to

dyspnea symptoms such that 59% of patients had NYHA functional class I or II symptoms at 30 days, which is slightly less compared with reports on patients with orthotopic valve replacement.[11,18] The change in KCCQ score was not significant in the present cohort, with a KCCQ score improvement of 7 points compared with an improvement of 19 points in patients undergoing orthotopic valve replacement.[11] However, patients included in the present trial were anatomically not suitable to receive orthotopic valve replacement in the first place, given their large annular diameters and more advanced right heart failure. It is known that right heart failure is one of the most deterministic factors for adverse outcomes in patients undergoing TTVI.[19] Despite preinterventionally optimized and intensified diuretic therapy, these patients had significantly elevated RA and left ventricular filling pressures, 2 factors that are associated with impaired outcomes and therapeutic response in TTVI.[20] Last with regard to KCCQ score, rejecting the nonsignificant result as a lack of improvement in KCCQ score might be a type II statistical error, as the sample size of 20 patients was not sufficiently powered to determine whether the observed difference was a true effect or rather seen by chance. Other studies investigating another heterotopic valve replacement systems have shown comparable improvements in dyspnea symptoms as assessed by NYHA functional class (postinterventional NYHA functional class I or II 50% vs 59% in the present study).[12] The symptomatic reductions for heterotopic approaches have recently been shown to be preserved up to 1 year after initial treatment.[21]

Heterotopic valve replacement is a therapy for patients with advanced disease stages, which is reflected by the present cohort having a median TRI-SCORE of 6 points, which is considered the highest risk category of the TRI-SCORE. The primary treatment goal in this population is symptom control, which heterotopic valve replacement achieves effectively. In a highly symptomatic population, congestion was relieved and symptoms diminished. Reduction in venous congestion and venous pressure by treating TR has been associated with improved survival.[13,14,17,20] Even in advanced disease, reducing venous congestion may improve outcomes after Trillium implantation. Selecting patients with severe edema, ascites, and hepatorenal syndrome could help identify those who benefit most. Unlike other TTVI approaches, heterotopic valve replacement is unaffected by chamber size or transtricuspid leads, as shown by a 100% success rate in a cohort in which one-third had prior failed TR treatments. Whether these hemodynamic and symptomatic benefits translate into better outcomes remains to be seen.

STUDY LIMITATIONS. The present trial is a first-in-human nonrandomized and unblinded study of 20 patients with relevant TR, and although it has shown a favorable early safety signal, long-term follow-up data are required to fully assess the safety of the device as well as the potential clinical benefit. Post-implantation syndrome has been seen in a significant proportion of patients (25%), but is an immune response that has not been associated with adverse outcomes in other situations, such as patients undergoing endovascular aortic repair,[22] but how this influences the course of patients with TR remains to be determined, as it is a significantly older population burdened by a high amount of comorbidities. There was no routine computed tomographic follow-up, but 12 patients underwent cardiac magnetic resonance imaging at 30 days, and another 2 patients underwent computed tomography at 8 and 18 months post-intervention, and no evidence for a stent fracture or other device-related complications was reported. Last, the study size limits its power, especially with regard to quality-of-life measures such as the KCCQ, and larger studies are needed to determine the effectiveness of the device with this regard.

CONCLUSIONS

The Trillium device is a heterotopic cross-caval transcatheter TV replacement device that allows the safe treatment of patients with symptomatic severe TR who have been deferred from other surgical or interventional therapeutic options. Early results have shown favorable symptomatic and hemodynamic responses, but whether this translates into improved long-term outcomes remains to be determined in properly powered clinical trials.

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PERSPECTIVES

WHAT IS KNOWN? Many patients with significant TR are not suitable candidates for interventional edge-to-edge repair or orthotopic valve replacement. In such cases, dedicated heterotopic valve replacement systems may offer a promising therapeutic alternative.

WHAT IS NEW? The Trillium device, a heterotopic valve replacement system, effectively improves hemodynamic parameters associated with backward failure and reduces symptoms in patients with significant TR. It also demonstrates a favorable safety profile at 30 days.

WHAT IS NEXT? The long-term effects and potential for sustained clinical benefits need to be evaluated in dedicated randomized controlled trials to determine whether these early improvements translate into favorable outcomes over time.

REFERENCES

1. Besler C, Unterhuber M, Rommel K-P, et al. Nutritional status in tricuspid regurgitation: implications of transcatheter repair. *Eur J Heart Fail*. 2020;22:1826–1836.

2. Kitamura M, Kresoja K-P, Balata M, et al. Health status after transcatheter tricuspid valve repair in patients with functional tricuspid regurgitation. *JACC Cardiovasc Interv*. 2021;14:2545–2556.

3. Kresoja K-P, Lauten A, Orban M, et al. Transcatheter tricuspid valve repair in the setting of heart failure with preserved or reduced left ventricular ejection fraction. *Eur J Heart Fail*. 2020;22:1817–1825.

4. Kodali S, Hahn RT, Makkar R, et al. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J*. 2023;44:4862–4873.

5. Ruf TF, Hahn RT, Kreidel F, et al. Short-term clinical outcomes of transcatheter tricuspid valve repair with the third-generation MitraClip XTR system. *JACC Cardiovasc Interv*. 2021;14:1231–1240.

6. Besler C, Orban M, Rommel K-P, et al. Predictors of procedural and clinical outcomes in patients with symptomatic tricuspid regurgitation undergoing transcatheter edge-to-edge repair. *JACC Cardiovasc Interv*. 2018;11:1119–1128.

7. Hagemeyer D, Merdad A, Sierra LV, et al. Clinical characteristics and outcomes of patients screened for transcatheter tricuspid valve replacement: the TriACT registry. *JACC Cardiovasc Interv*. 2024;17:552–560.

8. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438–1454.

9. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388:1833–1842.

10. Donal E, Dreyfus J, Leurent G, et al. Transcatheter edge-to-edge repair for severe isolated tricuspid regurgitation: the tri.fr randomized clinical trial. *JAMA*. 2025;333:124–132.

11. Kodali S, Hahn RT, George I, et al. Transfemoral tricuspid valve replacement in patients with tricuspid regurgitation: TRISCEND study 30-day results. *JACC Cardiovasc Interv*. 2022;15:471–480.

12. Estévez-Loureiro R, Sánchez-Recalde A, Amat-Santos IJ, et al. 6-Month outcomes of the TricValve system in patients with tricuspid regurgitation: the TRICUS EURO study. *JACC Cardiovasc Interv*. 2022;15:1366–1377.

13. Unterhuber M, Kresoja K-P, Besler C, et al. Cardiac output states in patients with severe functional tricuspid regurgitation: impact on treatment success and prognosis. *Eur J Heart Fail*. 2021;23:1784–1794.

14. Stolz L, Orban M, Besler C, et al. Cardiohepatic syndrome is associated with poor prognosis in patients undergoing tricuspid transcatheter edge-to-edge valve repair. *JACC Cardiovasc Interv*. 2022;15:179–189.

15. Kresoja K-P, Rosch S, Schöber AR, et al. Implications of tricuspid regurgitation and right ventricular volume overload in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2024;26(4):1025–1035. https://doi.org/10.1002/ejhf.3195

16. Orban M, Wolff S, Braun D, et al. Right ventricular function in transcatheter edge-to-edge tricuspid valve repair. *JACC Cardiovasc Imaging*. 2021;14:2477–2479.

17. Rommel K-P, Besler C, Noack T, et al. Physiological and clinical consequences of right ventricular volume overload reduction after transcatheter treatment for tricuspid regurgitation. *JACC Cardiovasc Interv*. 2019;12:1423–1434.

18. Wild MG, Lubos E, Cruz-Gonzalez I, et al. Early clinical experience with the TRICENTO bicaval valved stent for treatment of symptomatic severe tricuspid regurgitation: a multicenter registry. *Circ Cardiovasc Interv*. 2022;15:e011302.

19. Kresoja K-P, Rommel K-P, Lücke C, et al. Right ventricular contraction patterns in patients undergoing transcatheter tricuspid valve repair for severe tricuspid regurgitation. *JACC Cardiovasc Interv*. 2021;14:1551–1561.

20. Rommel K-P, Bonnet G, Fortmeier V, et al. Congestion patterns in severe tricuspid regurgitation and transcatheter treatment: Insights from a multicentre registry. *Eur J Heart Fail*. 2024;26(4):1004–1014. https://doi.org/10.1002/ejhf.3235

21. Blasco-Turrión S, Briedis K, Estévez-Loureiro R, et al. Bicaval TricValve implantation in patients with severe symptomatic tricuspid regurgitation: 1-year follow-up outcomes. *JACC Cardiovasc Interv*. 2024;17:60–72.

22. Zhu Y, Luo S, Liu Y, Huang W, Ding H, Luo J. Post-implantation syndrome after thoracic endovascular aortic repair for type B aortic dissection: a single-center experience with 646 cases. *Eur J Vasc Endovasc Surg*. 2019;58:e386–e387.

KEY WORDS heart failure, heart valve diseases, transcatheter heart valve therapies, tricuspid regurgitation

APPENDIX For a description of the Trillium device and its implantation, a supplemental table, figures, and a video, please see the online version of this paper.